A more descriptive title has been added and the specification has been reviewed and it is believed to be in good order. The comments in the Official Action with respect to the preferred arrangement of the specification has been noted.

Claims 2, 8, 13-15, 21-23, 34, 37-41, 45 and 46 have been canceled from the application without prejudice or disclaimer. New claim 50 has been added. The claims now remaining in the application are claims 1, 3-7, 9-12, 16-20, 24-33, 35, 36, 42-44 and 47-50. Applicants have canceled certain claims in an effort to expedite the prosecution to an early indication of allowable subject matter and retain all rights to the further prosecution of the canceled claims in a subsequent continuation application. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

With respect to the prior art, Applicants note that claims 25, 35, 36 and 48 have not been included in any prior art rejections and therefore these claims clearly contain allowable subject matter.

In particular, Applicants have amended the claims to restrict the claims to an assay in which the samples are contacted with a specific binding ligand which serves to separate **and concentrate** the Holo TC II from which the cobalamin is released and determined. The concentration allows the assay to be effected using automated procedures and the assay method itself is based on the concept that reduced Holo TC II is an effective indicator for vitamin B_{12} (i.e. cobalamin) deficiency. As previously noted, the restriction of the claims is simply in an effort to expedite the prosecution of the application to an early allowance and cancellation of claims or the further limitations to the claims to cover a particularly preferred assay technique is not to be construed to be an abandonment by the Applicants of the broader aspects or other aspects of the invention which will be pursued in subsequent patent applications.

The objection to claims 26 and 39 has been duly noted and corrected in the amendments to the claims. Accordingly, it is most respectfully requested that the claim objections in items 4 and 5 of the Official Action be withdrawn.

The rejection of claims 1-49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention has been carefully considered. Each of the enumerated items set forth on page 4 of the Official Action has been obviated by the amendment to these terms. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 1, 5-7,12, 41-43, 45-47 under 35 U.S.C. 102(b) as being anticipated by Quados et al. has been carefully considered but is most respectfully traversed.

Quados reports the production of monoclonal antibodies that bind to apo-TC II and/or holo TC II, i.e. TC II uncomplexed by or complexed by cobalamin. This discussion is in the context of inducing cobalamin depletion so as to impair cell replication by using an anti TC II monoclonal antibody to block membrane binding of holo TC II and hence impair cellular uptake of cobalamin. Quados does not disclose an assay for TC II-bound cobalamin in body fluid as defined in claim 1 of the present application, nor does Quados in any way suggest that such an assay would in any way be desirable. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 4 and 49 under 35 U.S.C. 103(a) as being unpatentable over Quados in view of Allen has been carefully considered but is most respectfully traversed for the reasons discussed above with respect to the Quados reference.

Allen is directed to a method of detecting folic acid or cobalamin deficiency which involves assessing cystathionine content in body fluid. Allen comments in columns 1 and 2 on earlier cobalamin assays stating that an "improved" assay had involved use of intrinsic factor for cobalamin binding but that this suffered from the problem of false positives for cobalamin deficiency and hence serum cobalamin should only be determined in patients showing symptoms typical of cobalamin deficiency. A further improved assay, mentioned in column 4 of Allen, involved assessing homocysteine and methylmalonic acid to predict cobalamin or folic acid deficiency. Thus, not only is there no suggestion in Allen that would lead the skilled person to expect that assessing holo

TC II might be a suitable way of assessing cobalamin deficiency, but the thrust of the developments reported in Allen is away from "direct" assessment of cabalamin or a bound form of cobalamin and towards indirect assessment by assessment of compounds which appear in the homocysteine metabolic pathway. It is therefore respectfully submitted that Allen alone or taken together with Quados does not point the skilled reader towards the present invention as claimed. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 27-33 under 35 U.S.C. 103 as unpatentable over Quados et al. in view of Hoyle et al. for the reasons set forth above with respect to the Quados et al. reference.

Applicants most respectfully submit that Hoyle is directed to a method of detecting cobalamin and involves a competitive binding assay involving contacting a body fluid sample with an anti-cobalamin antibody and would label the cobalamin. Again, in the introductory part, Hoyle refers to the "standard" technique for cobalamin assessment involving binding using intrinsic factor. The Hoyle method is clearly aimed at determining total cobalamin and would give the skilled reader no reason whatsoever to think of measuring only TC II-bound cobalamin. Accordingly, taken alone or in combination with Quados, Hoyle in no way suggests the assay method of the present invention. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claim 1, 5-7, 10, 12, 16-20, 23, 26 and 40-47 under 35 U.S.C. 103 as being unpatentable over McLean et al. in view of Houts as set forth in item 13 on page 7 of the Official Action has been carefully considered but is most respectfully traversed.

McLean, a publication for the Quados group, is once again concerned with provoking cobalamin deficiency in proliferating cells by the use of antibodies which bind to TC II. The anti-TC II antibodies used by McLean were the ones reported by Quados in reference 16. The teaching of McLean is towards the use of anti-TC II antibodies as drugs for the treatment of leukaemia. There is no suggestion that cobalamin deficiency could be assessed by assessing holo TC II. Moreover McLean suggests that holo-TC II may not alone be responsible for cobalamin uptake, in other words the reader would

not see McLean as teaching away from the standard total cobalamin assay towards a holo TC II alone assay.

Houts relates to intrinsic factor based competitive binding assays for total cobalamin and again, interestingly, in column 1, line 16 and following, positively teaches against the use of TC II as the basis for an assay. The skilled man, reading Houts would thus be given no incentive whatsoever to produce a TC II based assay for cobalamin. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 8-9, 11, 13-15, 21-22, 24 and 37-39 under 35 U.S.C. 103 as being unpatenable over McLean et al. in view of Houts and further in view of Herbert has been carefully considered but is most respectfully traversed. As previously noted, the combination of McLean et al. and Houts does not render obvious the presently claimed invention. As mentioned above, both McLean and Houts contain clear teachings away from holo TC II-based assays for cobalamin deficiency.

Applicants most respectfully submit that the Herbert et al. reference does not overcome the deficiencies of the primary reference. Herbert is concerned with separating TC II from TC I but contains no suggestion whatsoever that would lead to the **concentrating** separations according to amended claim 1 which, as discussed above, facilitate automation of the assay according to the invention. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicants wish to make of record the following two references cited in the international search report issued in connection with the corresponding international patent application. Copies of these documents are submitted herewith along with a Form 1449.

Nexoe describes antibodies directed to transcobalamin I and Rothenberg et al. discusses the structure and function of transcobalamin II and receptors therefor. Neither appears at all relevant to the present application.

In view of the above comments and further amendments to the specification and claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,
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REF:kdd
A01.wpd

July 27, 2000

B/O Form PTO-1449	Atty. Docket Number	Serial Number
U.S. Department of Commerce Patent and Trademark Office	REF/Sundrehagen/226	09/417,226
Information Disclosure Statement by Applicant	Applicant SUNDREHAGEN et al.	
	Filing Date October 13, 1999	Group 1641

U.S. Patent Documents

Examiner Initial		Document Number	Date	Patentee/Applicant	Class	Subclass	Filing Date if Appropriate

Foreign Patent Documents

Examiner Initial		Document Number	Publication Date	Country/Agency	Class	Subclass	Translation	
							Yes	No

Other Documents (Including Author, Title, Date, Pertinent Pages, Place of Publication, Etc.)

JA	ABSTRACT ONLY	Nexoe, Ebba, "Characterization of the cobalamins attached to transcobalamin I and transcobalamin II in human plasma", 1977, XP002127542
JA	ABSTRACT ONLY	Rothenberg S.P., Quadros E.V., "Transcobalamin II and the membrane receptor of the transcobalamin II-cobalamin complex", 1995, XP002127541

Examiner	Date Considered
	10/2000

EXAMINER: Initial if citation is considered, whether or not citation is in conformance with MPEP 609; Draw a line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.